The Association of Calcium and Vitamin D with Risk of Colorectal Adenomas

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ABSTRACT The Polyp Prevention Trial (PPT) was a multicenter randomized clinical trial designed to determine the effects of a high-fiber, high-fruit and vegetable, low-fat diet on the recurrence of adenomatous polyps in the large bowel. Detailed dietary intake and supplement use data were collected at baseline and at each of 4 annual study visits. Adenoma recurrence was ascertained by complete colonoscopy at baseline and after 1 and 4 y. Recurrence was found in 754 of the 1905 trial participants. We evaluated the association between calcium and vitamin D intake and adenomatous polyp recurrence after adjusting for intervention group, age, gender, nonsteroidal anti-inflammatory drug use, total energy intake, and the interaction of gender and intervention group. Vitamin D models were also adjusted for the location of the clinic site. Dietary variables were adjusted for total energy intake via the residual method. There were no overall significant associations between adenoma recurrence and dietary calcium intake [odds ratio (OR) for the 5th compared with the lowest quintile = 0.91; 95% CI = 0.67–1.23; *P*-trend = 0.68], total calcium intake (OR = 0.86; 95% CI = 0.62–1.18; *P*-trend = 0.20), or dietary vitamin D intake (OR = 0.93; 95% CI = 0.69–1.25; *P*-trend = 0.43) averaged over follow-up. Total vitamin D intake was weakly inversely associated with adenoma recurrence (OR = 0.84; 95% CI = 0.62–1.13; *P*-trend = 0.03). Supplemental calcium and vitamin D use during follow-up also were inversely associated with adenoma recurrence (OR for any compared with no use = 0.82; 95% CI = 0.68–0.99; and OR = 0.82; 95% CI = 0.68–0.99; for calcium and vitamin D, respectively). Slightly stronger associations were noted for the prevention of multiple recurrences. Our analyses did not suggest a significant effect modification between total calcium and total vitamin D intake (*P* = 0.14) on risk for adenoma recurrence. This trial cohort provides some evidence that calcium and vitamin D may be inversely associated with adenoma recurrence. J. Nutr. 135: 252–259, 2005.

KEY WORDS: • *calcium* • *vitamin D* • *Polyp Prevention Trial* • *colorectal adenomas*

Evidence from experimental, animal, and human studies accumulated over the past 2 or more decades has suggested a role for calcium, and more recently vitamin D, in colorectal cancer incidence. The evidence suggests that calcium and vitamin D may reduce colorectal cancer risk via a number of mechanisms including binding of long-chain fatty acids and bile acids in the small intestine and protecting colonic epithelial cells from mutagens as well as effects on cell proliferation and differentiation, apoptosis, angiogenesis, and cell cycle regulation (1).

Several large prospective cohort studies reported that individuals with calcium intakes beginning at ~700 mg/d are protected from colon cancer compared with those with more limited consumption (2–4). In contrast, a meta-analysis including 24 case-control and cohort studies concluded that the existing data did not support the hypothesis that calcium reduced the risk for colorectal cancer (5).

Two recently published review articles concluded that the available research suggested a protective effect for vitamin D on colon cancer risk (6,7). Epidemiologic studies suggest that

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the effects of calcium and vitamin D on risk may differ appreciably by several factors including gender, total dietary fat intake, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).[3] For example, the large prospective Cancer Prevention Study II Nutrition Cohort (3) recently reported that the relative risk (RR) of colorectal cancer was inversely associated with total vitamin D consumption, with stronger results apparent among men (RR = 0.71; 95% CI = 0.51–0.98 for the highest compared with the lowest quintile).

Results from randomized clinical trials to evaluate the effects of calcium on adenoma recurrence suggested that there may be a role for calcium in the prevention of recurrent adenomas (8,9). These are important findings because the majority of colorectal cancers are thought to originate as adenomatous polyps (10,11). In addition, some recent studies suggested that calcium and vitamin D may act synergistically to protect against recurrence of adenomas. For example, the Calcium Polyp Prevention Study (12) reported that calcium supplementation reduced the risk for adenoma recurrence only in participants with higher serum levels of 25-hydroxyvitamin D.

Although a number of previous studies evaluated the relation between calcium and vitamin D and adenoma recurrence, the results are not conclusive, and many studies did not evaluate the joint effects of calcium and vitamin D. The Polyp Prevention Trial (PPT), a multicenter randomized clinical trial, was designed to determine the effects of a high-fiber, high-fruit and -vegetable, low-fat diet on the recurrence of adenomatous polyps in the large bowel; therefore, high-quality detailed dietary and supplement data were collected annually for all participants throughout the trial and were available for analysis (13). In addition, the PPT data provided the opportunity to examine effect modification by fat, fiber, phosphorous, gender, site, and NSAID use in a large prospective study.

SUBJECTS AND METHODS

Sample population. The overall design, rationale, dietary intervention and endpoint procedures, and trial results for the PPT were reported previously (14–16). Briefly, the study recruited 2079 men and women ≥35 y of age between 1991 and 1994 at 8 clinical centers in the United States (listed in the Appendix). Participants had to have had 1 or more histologically confirmed colorectal adenomas identified by complete colonoscopy in the 6 mo before randomization. To be eligible, potential subjects must not have had resected adenomatous polyps previously, nor could they have been diagnosed with colorectal cancer, inflammatory bowel disease, or a polyposis syndrome. In addition, participants had to be ≤150% of their recommended weight and could not be currently using lipid-lowering medications. The study was approved by the Institutional Review Boards of the National Cancer Institute and each of the participating centers. All participants provided written informed consent at entry into the study.

At baseline and each of 4 annual follow-up visits, participants completed an interviewer-administered questionnaire including demographic, clinical, medication use, and dietary and supplement information and provided a blood sample after fasting for analysis of total cholesterol, carotenoids, and other biomarkers of interest. Baseline FFQ and 4-d food records were viewed before randomization to ensure that the participants' dietary patterns were not already similar to the intervention plan and to gauge the participants' ability to comply with recording dietary intake data (13). After randomization, intervention participants received instruction in the implementation of the PPT high-fiber [18 g/1000 kcal (4186 kJ)], high-fruit and -vegetable (5–8 servings/d), low-fat (20% of total energy) dietary plan; control participants received printed material on healthy eating, but no further information on diet from the study. A detailed description of the intervention and the dietary changes achieved was published previously (13). For the present study, 1905 participants who completed the full trial follow-up were evaluated.

Assessment of dietary intake and supplement use. Diet was assessed at baseline and annually with a modified Block-National Cancer Institute (NCI) FFQ (17) and a subset completed 4-d food records. Before the collection of the dietary data, participants viewed instructional videos demonstrating food portion size estimates and received instruction in the completion of the dietary instruments. The FFQ queried usual food consumption patterns over the past year, and was used in the present analysis. Data on the vitamin D content of foods included in the FFQ were unavailable in the database; thus we collected values from the USDA, current literature, and product labels and added this information to the database routinely used for nutritional analysis of the modified Block-NCI FFQ, Dietsys version 3.7. Participants were asked to bring all currently used prescription and nonprescription medications, including dietary supplements, to each annual visit, and information about the name, dosage, and frequency of use was recorded. Data on calcium and vitamin D intake from all multivitamin and mineral supplements, individual supplements, and medications (e.g., antacids) were totaled for each annual visit. In this study, 68% of supplemental calcium users obtained calcium from multivitamin and mineral supplements, 26% obtained calcium from individual calcium supplements, 6% obtained calcium from a calcium/vitamin D supplement, and 1% obtained calcium from a mixed-mineral supplement without vitamin D. For vitamin D supplement users, 89% obtained vitamin D from a multivitamin and mineral supplement, 7% used a calcium/vitamin D combination supplement, and 4% reported using a supplement containing vitamin D alone or with 1 or 2 other vitamins.

Assessment of adenomas. Participants received full colonoscopies at baseline, their 1-y visit, and at the end of the trial intervention, ~4 years after randomization. The colonoscopy at the 1st annual visit allowed for the detection and removal of any lesions missed by the baseline procedure. Pathologically confirmed adenomas diagnosed in between the 1-y visit and the end of trial colonoscopy, inclusive, were considered recurrent adenomas. For participants who completed the baseline but missed the 1-y follow-up colonoscopy, recurrent adenomas were those detected at least 2 y after randomization. A total of 754 participants had recurrent adenomas during follow-up. Biopsy samples of all adenomas removed during colonoscopy were reviewed independently by 2 pathologists to determine histological features and degree of atypia. Information on the size, number, and location of all lesions detected by colonoscopy was abstracted from endoscopy reports. Advanced adenomas were those that had a maximal diameter ≥ 1 cm or had at least 25% villous elements or displayed evidence of high-grade dysplasia; these adenomas are generally considered to be more strongly associated with invasive colorectal cancer.

Statistical analyses. Statistical analyses were performed using Statistical Analysis Systems (SAS) software (18,19). The characteristics of participants with and without recurrent adenomas were compared by t tests for continuous variables, and χ^2 test for categorical variables. Odds ratios (ORs) and 95% CIs for the association between adenoma recurrence and calcium and vitamin D variables were determined in logistic regression models. Dietary variables were adjusted for total energy intake via the residual method of Willett and Stampfer (20). Data for dietary and supplement variables from all FFQs before the y 4 colonoscopy, (baseline, y 1, 2, and 3) were averaged for all participants. Because the PPT was a dietary intervention trial, the baseline diet was likely different from follow-up, particularly for the intervention participants. To develop categorical variables, dietary and total calcium and vitamin D variables were grouped into quintiles based on the distribution among the study population without missing endpoints and were entered into models as indicator variables defined by the 2nd through 5th quintiles of intake, with the lowest quintile as the referent group. To conduct linear trend tests across levels of nutrients, we created variables using exposure scores based on the median values for each quintile, and

[3] Abbreviations used: DRI, Dietary Reference Intake; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPT, Polyp Prevention Trial; PTH, parathyroid hormone; RR, relative risk.

used these in logistic regression models. Supplement variables for calcium and vitamin D were characterized in 3 ways for analysis: *1*) added as amount of supplement to dietary data to create total intake variables; *2*) used as indicator variables for any supplement use during any of the time periods used for analysis; and *3*) added as 2 indicator variables for the upper 2 tertiles of intake (below and above the median intake among supplement users), with no use as a referent. We also characterized participants who reported supplement use at all of their visits included in the analyses as "persistent" users and compared them with those who did not report consistent use at every visit in secondary analyses. In addition to the main analysis evaluating the relation between nutrients and any adenoma recurrence during the trial, we also evaluated associations with multiple adenoma recurrence and advanced adenoma recurrence in logistic regression models. In the former (multiple), the comparison group comprised those with a single or no adenoma recurrence, and in the latter (advanced), the comparison group comprised those with recurrent nonadvanced adenomas or no recurrent adenomas. Additional analyses were conducted with only those participants who developed a recurrent adenoma, with outcome defined as having multiple recurrent adenomas or having advanced recurrent adenomas vs. single or nonadvanced recurrences, respectively.

Associations between selected calcium and vitamin D variables and site of recurrence were evaluated by designating the site of recurrence within the bowel as either proximal or distal (including rectal) with the no adenoma recurrence group as the referent in each case. Potential confounders were evaluated by assessing their associations with calcium and vitamin D variables and adenoma recurrence. Final models were adjusted for intervention group, age, gender, total energy intake, NSAID use, and the interaction of gender and intervention group. NSAID use was collected in a number of different ways in the PPT, including baseline, ever/never, and consistent use of NSAIDs during the trial; we evaluated the effects of each of these variables during our analyses. For the final analyses, NSAID use was coded as an indicator variable for any or no use (referent) at baseline of aspirin and other nonaspirin NSAIDS such as ibuprofen, naproxen, indomethacin, or piroxicam, as discussed in a previous analysis (21). For the vitamin D analyses, a variable for greater sunlight exposure was created for the PPT trial clinics located in warmer climates (i.e., Oakland, CA; Wake Forest, NC; and Washington, DC) and was also included as a covariate. We also evaluated the risk estimates when calcium was included as a covariate in the vitamin D models and vice versa and considered including history of multiple adenomas (yes/no) at baseline as a covariate in the multivariate models; however, because the addition of these variables did not appreciably change our risk estimates for the exposures of interest, we chose not to include them in the final models.

Effect modification by gender, NSAID use, intervention group assignment, and fiber, phosphorous, folate, fat intake, and calcium (for vitamin D) or vitamin D (for calcium) was assessed by including the individual factor (e.g., gender) and its cross-product term with the continuous total calcium (e.g., continuous total calcium × gender) or supplement variables (e.g., continuous calcium supplement × gender) or the continuous total vitamin D or vitamin D supplement variables in separate multivariate models for each potential effect modifier of interest. When significant, meaningful interactions were found, analyses were repeated stratified at the median for the effect modifier. All statistical analyses were two-sided and *P*-values were considered to be significant if <0.05.

RESULTS

Descriptive characteristics of study participants are presented in **Table 1**. The majority of PPT participants were Caucasian, 64% were men, and 75% reported completing at least some education beyond high school. The mean age among participants was 61.1 y and the mean BMI was 27.6 kg/m^2. Approximately one third of study participants reported baseline NSAID use. Mean intakes for total calcium and total vitamin D were lower than levels recommended by the Food and Nutrition Board's Dietary Reference Intakes (DRIs) (22). Approximately half of the trial participants reported using a supplement or medication containing calcium or vitamin D at least once during follow-up; however, few PPT participants

TABLE 1

Selected characteristics of Polyp Prevention Trial participants by adenoma recurrence[1,2]

Characteristic	Overall (n = 1905)	Any polyp recurrence (n = 754)	No polyp recurrence (n = 1151)	*P*-value[3]
Age, *y*	61.1 ± 9.9	62.8 ± 9.2	59.9 ± 10.1	<0.0001
BMI, *kg/m*2	27.6 ± 3.9	27.8 ± 3.9	27.4 ± 4.0	0.04
Gender, % *male*	64	72	60	0.01
Race, % *Caucasian*	90	90	90	0.97
Education, % ≤ *high school*	25	26	24	0.50
Family history of colorectal cancer, % *yes*	27	27	27	0.77
Use NSAIDs, % *yes*	34	31	35	0.11
Total energy, *kJ/d*	7779 ± 1863	7846 ± 1930	7733 ± 1821	0.19
Total calcium, *mg/d*	981 ± 435	958 ± 432	995 ± 437	0.07
Dietary calcium, *mg/d*	853 ± 342	856 ± 365	850 ± 326	0.72
High-fat dairy, *g/d*	119 ± 137	122 ± 145	116 ± 132	0.36
Low-fat dairy, *g/d*	214 ± 210	213 ± 223	214 ± 201	0.87
Calcium supplements, % *any*	52	48	55	0.003
Calcium supplements,[4] % *mg/d*	248 ± 326	216 ± 284	267 ± 346	0.02
Total vitamin D, *μg/d*	8.2 ± 14.5	7.9 ± 16.8	8.4 ± 12.8	0.52
Dietary vitamin D, *μg/d*	4.4 ± 2.4	4.4 ± 2.6	4.4 ± 2.2	0.60
Vitamin D supplements, % *any*	47	44	50	0.01
Vitamin D supplements,[4] *μg/d*	8.1 ± 20.0	8.0 ± 24.4	8.1 ± 16.9	0.97
Vitamin D and calcium supplements, % *any of both*	46	43	48	0.01

[1] Results are means ± SD for continuous variables and % for categorical variables.
[2] Adenomatous polyp recurrence diagnosed through postintervention at y 4.
[3] *P*-values for differences in means were determined by *t* test and differences in proportions were determined by χ^2 test.
[4] Among supplement users.

reported supplement use at levels greater than the DRIs or levels used in supplement trials with adenoma recurrence as an outcome. Only 24 participants (2 recurrences, 22 nonrecurrences) reported calcium supplement use ≥ 1200 mg/d; 120 participants (37 recurrences, 83 nonrecurrences) reported supplemental vitamin D use ≥ 10 μg/d. Calcium and vitamin D intakes were significantly correlated in this population. Among all participants, total calcium and vitamin D intake had a Spearman correlation coefficient of 0.69 ($P < 0.001$), and dietary calcium and vitamin D intake had a Spearman correlation coefficient of 0.85 ($P < 0.001$). Among participants who reported using both types of supplements, correlation coefficients for total and dietary calcium and vitamin D were 0.55 ($P < 0.001$) and 0.84 ($P < 0.001$), respectively.

In logistic regression analyses, no significant associations existed between overall adenoma recurrence, multiple recurrence, or advanced recurrence and dietary or total calcium intake (**Table 2**) or consumption of low- or high-fat dairy products (data not presented). Any calcium supplement use was significantly inversely associated with both recurrence (OR = 0.82; 95% CI = 0.68–0.99) and multiple recurrence (OR = 0.74; 95% CI = 0.58–0.95). The tertile analysis for calcium supplement use showed a marginal dose response for recurrence (*P*-trend = 0.07) and a significant dose-response relation for multiple recurrence (*P*-trend = 0.01). The aforementioned recurrence outcomes and dietary vitamin D intake were not significantly associated (**Table 3**). Total vitamin D intake was weakly associated with both adenoma recurrence and multiple recurrences. In both cases, the risk estimates (ORs) comparing the highest and lowest quintiles of intake were protective with significant *P*-trend tests, but both sets of 95% CIs were included 1.0 (Table 3). Any supplemental vitamin D use was also significantly inversely associated with both recurrence (OR = 0.82; 95% CI = 0.68–0.99) and multiple recurrence (OR = 0.73; 95%CI = 0.53–0.99). For vitamin D supplement use, the tertile analysis showed a significant dose response for both recurrence ($P = 0.04$) and multiple recurrence ($P = 0.04$). The associations for both calcium and vitamin D supplement use remained after adjustment for multivitamin use. We also evaluated baseline intake alone for total, dietary, and supplemental calcium and vitamin D. Overall, the results were consistent with those reported for the variables averaged over time (data not presented). Last, in subgroup analyses, the associations between calcium and vitamin D supplement use were stronger when persistent use over time was used to define supplement variables (for any recurrence OR = 0.72; 95% CI = 0.55–0.93 for persistent calcium use and OR = 0.74; 95% CI = 0.57–0.97 for persistent vitamin D use).

Table 4 shows the multivariate ORs with 95% CIs for adenoma recurrence stratified by site of recurrence. There were no meaningful differences in calcium or vitamin D associations with adenoma risk by site of recurrence. The associations between calcium intake and adenoma risk did not differ by intake of dietary fat, fiber, or phosphorus intake at baseline or averaged over time, or by NSAID use, intervention group assignment, or gender (not presented). The associations between vitamin D and recurrence were not meaningfully different by these factors, with the exception of intervention assignment. We did observe significant effect modification between vitamin D supplement use and intervention group assignment for risk of recurrence ($P = 0.02$). This was not significant for either advanced or multiple adenoma recurrence; however, the stratified (control/intervention) risk estimate patterns for advanced and multiple adenoma recurrence were similar to those for any adenoma recurrence. Among the control group, the multivariate OR for any use of supplemental vitamin D was 0.71 (0.54–0.92) compared with 0.95 (0.73–1.24) for the intervention group (data not presented). Our analyses did not suggest significant effect modification between total calcium and total vitamin D intake ($P = 0.14$) on the risk for adenoma recurrence. The risk estimates and 95% CIs for adenoma recurrence for low-calcium/high-vitamin D, high-calcium/low-vitamin D, and high-calcium/high-vitamin D compared with low-calcium/low-vitamin D (based on median splits) were 0.76 (0.55–1.04), 1.23 (0.89–1.69), and 0.87 (0.70–1.09), respectively.

TABLE 2

Multivariate-adjusted OR and 95% CI for colorectal polyp recurrence with consumption of calcium from diet and supplements[1]

Quintile/category	Range	Cases (n = 754)	Recurrence OR (95% CI)	Cases (n = 125)	Advanced OR (95% CI)	Cases (n = 318)	Multiple OR (95% CI)
Dietary Ca, *mg/d*	<635	160	1.0	25	1.0	63	1.0
2	635–763	152	0.98 (0.72–1.32)	20	0.83 (0.45–1.55)	62	1.00 (0.67–1.48)
3	764–888	140	0.83 (0.61–1.12)	25	1.02 (0.56–1.86)	63	0.98 (0.68–1.47)
4	889–1048	159	1.04 (0.77–1.40)	30	1.23 (0.69–2.19)	70	1.17 (0.79–1.74)
5	1048	143	0.91 (0.67–1.23)	25	1.04 (0.57–1.90)	60	1.01 (0.67–1.51)
P-trend			0.68		0.58		0.77
Supplemental Ca, *mg/d*							
None		391	1.0	70	1.0	177	1.0
Any		363	0.82 (0.68–0.99)	55	0.73 (0.50–1.07)	141	0.74 (0.58–0.95)
1	0	391	1.0	70	1.0	177	1.0
2	≤133	185	0.82 (0.65–1.03)	17	0.45 (0.26–0.78)	77	0.79 (0.59–1.07)
3	>133	178	0.83 (0.65–1.05)	38	1.07 (0.69–1.65)	64	0.68 (0.49–0.94)
P-trend			0.07		0.77		0.01
Total Ca, *mg/d*							
1	<666	156	1.0	23	1.0	58	1.0
2	666–814	163	1.12 (0.83–1.51)	26	1.19 (0.66–2.16)	73	1.33 (0.90–1.96)
3	815–969	154	1.02 (0.76–1.38)	22	1.00 (0.54–1.85)	71	1.29 (0.87–1.92)
4	970–1226	150	1.00 (0.74–1.36)	23	1.56 (0.88–2.77)	69	1.30 (0.87–1.93)
5	>1226	131	0.86 (0.62–1.18)	21	0.93 (0.49–1.79)	47	0.88 (0.56–1.36)
P-trend			0.20		0.98		0.36

[1] Adjusted for age, NSAID use, gender, total energy intake, intervention assignment, and gender × intervention group.

TABLE 3

Multivariate-adjusted OR and 95% CI for colorectal polyp recurrence with consumption of vitamin D from diet and supplements[1]

Quintile/category	Range	Cases (n = 754)	Recurrence OR (95% CI)	Cases (n = 125)	Advanced OR (95% CI)	Cases (n = 318)	Multiple OR (95% CI)
Dietary vitamin D, $\mu g/d$							
1	<2.75	158	1.0	18	1.0		1.0
2	2.75–3.65	149	0.92 (0.72–1.32)	27	1.59 (0.85–2.99)	60	1.22 (0.97–1.01)
3	3.66–4.60	155	0.97 (0.68–1.24)	20	1.11 (0.57–2.16)	70	0.97 (0.65–1.45)
4	4.61–5.95	140	0.78 (0.72–1.31)	31	1.63 (0.88–3.03)	60	1.01 (0.67–1.50)
5	>5.95	152	0.93 (0.69–1.25)	29	1.56 (0.84–2.93)	64	1.01 (0.68–1.51)
P-trend			0.43		0.20	64	0.74
Supplemental vitamin D, $\mu g/d$							
None		425	1.0	74	1.0	191	1.0
Any		329	0.82 (0.68–0.99)	51	0.78 (0.53–1.13)	127	0.72 (0.56–0.93)
1	0	425	1.0	74	1.0	191	1.0
2	≤6.22	163	0.85 (0.67–1.08)	20	0.62 (0.37–1.04)	60	0.72 (0.52–0.99)
3	>6.22	166	0.80 (0.63–1.00)	31	0.93 (0.60–1.45)	77	0.73 (0.53–0.99)
P-trend			0.04		0.50		0.02
Total vitamin D, $\mu g/d$							
1	<3.35	158	1.0	23	1.0	66	1.0
2	3.36–4.90	176	1.22 (0.91–1.65)	27	1.15 (0.64–2.06)	80	1.23 (0.85–1.79)
3	4.91–7.05	148	0.87 (0.65–1.18)	22	0.88 (0.47–1.62)	64	0.90 (0.61–1.34)
4	7.06–11.70	131	0.77 (0.56–1.02)	22	0.94 (0.50–1.74)	57	0.83 (0.56–1.24)
5	>11.70	141	0.84 (0.62–1.13)	31	1.34 (0.76–2.39)	51	0.70 (0.47–1.06)
P-trend			0.03		0.31		0.01

[1] Adjusted for age, NSAID use, gender, total energy intake, intervention assignment, location of clinical center, and gender × intervention group.

DISCUSSION

In the PPT we found no significant associations between any of the adenoma recurrence outcome variables we evaluated and dietary or total calcium intake, consumption of low- or high-fat dairy products, or dietary vitamin D intake. Total vitamin D intake was inversely associated with overall recurrence. In addition, inverse associations were observed for both calcium and vitamin D supplementation with both single and multiple adenoma recurrences.

Previous epidemiologic studies found protective effects for calcium and vitamin D with the risk of colorectal cancer and adenomatous polyps, but results were inconsistent (6,23–47). A meta-analysis conducted in 1996, including data from 24 published reports, reported a nonsignificant summary RR of 0.89 with a 95% CI of 0.79–1.01 (6) for the association of total calcium with the risk of colorectal cancer. Since that time, results from case-control and prospective cohort studies have continued to be mixed (4,23–30). For example, the large population-based, case-control study of Kampman et al. (23) found that calcium was inversely associated with colon cancer risk overall (OR 0.6; 95% CI = 0.5–0.9) and among participants of both genders. Wu and colleagues (4) evaluated the association between calcium intake and colon cancer in the Nurses' Health Study and the Health Professionals' Follow-up Study in pooled analyses including >1000 cancer cases. Overall, the protective effects for total calcium among those in the highest compared with the lowest quintiles of intake were stronger among men (RR = 0.64; 95% CI = 0.43–0.95) than women (RR = 0.94; 95% CI = 0.66–1.33). Their results suggested that among participants with high dietary intakes, no further benefits were observed for calcium supplement use. Their results also showed protective effects for higher total calcium intakes for distal (RR = 0.65; 95% CI 0.43–0.98), but not proximal colon cancer. McCullough and colleagues (3) observed in the Cancer Prevention Study II Nutrition Cohort that total calcium intake was only marginally associated with lower colorectal cancer risk, although there was a significant trend across increasing quintiles of intake (P = 0.02); however, a stronger relation was observed for supplemental calcium at levels ≥ 500 mg/d (RR = 0.69; 95% CI 0.49–0.96). A large prospective study of Norwegian men and women (n = 50,535) reported no association between colorectal cancer and calcium intake (28); however, compared with the previously mentioned cohort analyses, this population was younger and fewer colon cancer cases were available for analysis (n = 143). Last, a recently published pooled analysis of 10 cohort studies including 4992 incident colorectal cancer cases reported that intake of milk, dietary calcium, and total calcium were significantly related to a reduced risk of colorectal cancer, with the stronger results noted for calcium from all sources (30).

Several observational epidemiology studies (31–40) and clinical trials (8,9,12,41–45,47,48), although not all (33,46) observed that increased calcium intake may play a role in preventing the development of colorectal adenomas. Our results are consistent with the results observed in calcium trials in which risk estimates ranged from 0.6 to 0.8, and were generally stronger when multiple recurrences were considered (9,40). Baron and co-workers (9,47) led the first large multicenter, randomized, double-blind clinical trial to evaluate whether an elemental calcium supplement (1200 mg) would reduce the rate of recurrence of colorectal adenomas. A total of 930 participants underwent follow-up colonoscopies 1 and 4 y after randomization to either calcium supplement or placebo control. A significant reduction in risk of recurrent colorectal adenomas was observed in the intervention compared with the control group (RR = 0.81; 95% CI 0.60–0.96) overall and for several subgroups, including advanced adenomas (RR = 0.65; 95% CI 0.46–0.93). Calcium supplementation had a more pronounced effect among those with lower dietary fat intakes. Calcium supplementation at 2000 mg/d was associated with a nonsignificant reduction in the risk of adenoma recurrence (RR = 0.66; 95% CI = 0.38–1.17) in another smaller (n = 665) intervention trial (8). This trial

TABLE 4

Multivariate-adjusted OR and 95% CI for colorectal polyp recurrence with consumption of calcium and vitamin D from diet and supplements stratified by recurrence site[1]

Quintile/category	Range	Cases (n = 517)	Proximal (right) OR (95% CI)	Cases (n = 367)	Distal (left) OR (95% CI)
Dietary calcium, *mg/d*					
1	<2.75	106	1.0	70	1.0
2	2.75–3.65	100	0.94 (0.67–1.31)	80	1.25 (0.87–1.81)
3	3.66–4.60	95	0.86 (0.61–1.20)	70	1.05 (0.72–1.54)
4	4.61–5.95	121	1.25 (0.90–1.73)	74	1.14 (0.78–1.67)
5	>5.95	95	0.92 (0.65–1.29)	73	1.18 (0.81–1.72)
			0.93		0.58
Supplemental calcium, *mg/d*					
None		279	1.0	196	1.0
Any		238	0.78 (0.63–0.96)	171	0.78 (0.62–0.99)
Total calcium, *mg/d*					
1	<666	102	1.0	72	1.0
2	666–814	106	1.04 (0.75–1.45)	83	1.25 (0.87–1.79)
3	815–969	119	1.27 (0.92–1.77)	65	0.94 (0.64–1.38)
4	970–1226	106	1.10 (0.79–1.53)	81	1.27 (0.88–1.83)
5	>1226	84	0.87 (0.61–1.24)	66	1.03 (0.69–1.52)
P-trend			0.38		0.97
Dietary vitamin D, *μg/d*					
1	<2.75	100	1.0	77	1.0
2	2.75–3.65	97	0.96 (0.69–1.35)	77	1.00 (0.70–1.44)
3	3.66–4.60	106	1.06 (0.76–1.49)	74	0.96 (0.67–1.38)
4	4.61–5.95	105	1.01 (0.72–1.41)	70	0.87 (0.60–1.26)
5	>5.95	109	1.09 (0.78–1.52)	69	0.89 (0.61–1.29)
P-trend			0.56		0.39
Supplemental vitamin D, *μg/d*					
None		301	1.0	213	1.0
Any		216	0.78 (0.63–0.96)	154	0.79 (0.62–0.99)
Total vitamin D, *μg/d*					
1	<3.35	104	1.0	79	1.0
2	3.36–4.90	122	1.24 (0.90–1.72)	86	1.11 (0.78–1.58)
3	4.91–7.05	111	1.05 (0.75–1.45)	64	0.76 (0.52–1.10)
4	7.06–11.70	86	0.78 (0.55–1.10)	72	0.92 (0.64–1.32)
5	>11.70	94	0.86 (0.61–1.20)	66	0.82 (0.56–1.18)
P-trend			0.04		0.21

[1] Adjusted for age, NSAID use, gender, total energy intake, intervention assignment, location of clinical center (vitamin D variables only), and gender × intervention group.

reported a protective association for calcium supplementation with adenoma recurrence in the proximal colon. Our analysis and that of Baron's group (9,47) did not find effect modification by recurrence location.

Martinez and colleagues (41) from the Wheat Bran Fiber trial reported that higher calcium intakes reduced risk for adenoma recurrence by ~40%. In contrast to what we observed, risk reduction appeared to be related to dietary rather than supplemental intake of calcium. Hyman and colleagues (42) reported an inverse association for dietary (OR = 0.72; 95% CI 0.43–1.22) and no association for supplemental calcium intake in their trial-based prospective study. There was an interaction between fat and calcium in the opposite direction to that reported by the trial of Baron et al. (9,47); calcium intake was more protective among those with higher fat intakes.

Several studies observed inverse associations for risk of colorectal cancer or adenomatous polyps with higher levels of vitamin D. Lieberman and colleagues (35) observed that vitamin D was inversely associated with a risk for advanced colonic neoplasia, defined as either invasive cancer or advanced adenomas (larger, villous, or with high-grade dysplasia). For those with intakes in the highest quintile of vitamin D, risk was estimated at 0.61 (0.39–0.99) compared with those with intakes in the lowest quintile. Martinez and colleagues (41) reported a nonsignificant protective association for dietary vitamin D intake (OR = 0.78; 95% CI = 0.78–1.13 for the highest quintile of intake) and no association for supplementary vitamin D intake (OR = 1.05; 95% CI 0.54–1.13 for the highest tertile of use) with recurrence of adenomas in their study. The authors noted that vitamin D levels in their Arizona-based study may have been more homogeneous than among other populations due to higher sunlight exposure.

Our data do not provide additional evidence that fat or phosphorous intakes are important modifiers of the relation between calcium and adenoma recurrence. The Calcium Polyp Prevention Study (47) reported that higher dietary fat attenuated the effect of calcium on adenoma recurrence; however, several studies also reported no effect or a more pronounced inverse association among those with higher dietary fat consumption (7). The latter studies are consistent with the hypothesis that calcium forms insoluble complexes in the colon, protecting colonic epithelial cells from mutagens. In contrast, Wallace et al. (47) speculated that dietary fat in the colon interferes with calcium absorption, particularly from supplemental sources. Wu et al. (4) also noted the suggestion of a more pronounced protective association for calcium and colon cancer risk among participants with lower phosphorous intake and speculated that higher phosphorous intakes may limit the intestinal absorption of calcium due to increased production of

insoluble calcium phosphates. Higher serum phosphate levels attenuate the synthesis of 1,25 dihydroxyvitamin D from 25-hydroxyvitamin D, decreasing calcium absorption and upregulating the synthesis of parathyroid hormone (PTH) (49). A recent review by McCarthy (48) notes that receptors for PTH are present in many precancerous lesions.

We observed that the protective association between supplemental vitamin D and adenomatous polyp recurrence was more apparent among control group participants. It is possible that the diet consumed by the intervention group obscured the modest protective effect of supplemental vitamin D in that group. There are a number of intervention-related dietary differences between the intervention and control group participants in this study. For example, the intervention group participants consumed diets lower in fat, higher in fiber, and higher in fruits and vegetables and the nutrients and phytochemicals common to fruits and vegetables. Our evaluation of potential effect modification by fat and fiber intake suggests that neither explains why the association between vitamin D supplement use and adenomatous polyp recurrence would be stronger among the control group. We did not evaluate potential effect modification by the wide range of antioxidant nutrients and phytochemicals found in fruits and vegetables. Last, we evaluated a number of potential effect modifiers in these analyses; therefore, these findings should be interpreted cautiously and further explored in other analyses.

There are several strengths of this study, including the prospective design, the large number of participants available for analysis, and the high-quality and comprehensive outcome data as well as dietary and supplement data collected throughout follow-up. In addition, participants of the PPT were recruited from a number of clinic locations across the United States. In this data set, calcium and vitamin D were fairly highly correlated with each other; therefore, it is worth noting the possibility of confounding. It is possible that this study may not be generalizable to all populations that experience adenomatous polyps. For example, 90% of the PPT participants were Caucasian, the majority completed high school or more education, and all had to meet the health-related eligibility criteria for the trial. Participants with a diagnosed risk factor for colorectal cancer may also be more health conscious than the general population.

In summary, our results are consistent with weakly protective associations for calcium and vitamin D with risk for recurrence of adenomatous polyps. The protective associations for these 2 nutrients were of similar magnitude among those with multiple adenoma recurrences, stronger for more persistent users of these supplements; for vitamin D supplements, the association was stronger among participants in the control group.

LITERATURE CITED

1. Lamprecht, S.A. & Lipkin, M. (2001) Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. Ann. N.Y. Acad. Sci. 952;73–87.

2. Bostick, R. M., Potter, J. D., Sellers, T. A., McKenzie, D. R., Kushi, L. H. & Folsom, A. R. (1993) Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. Am. J. Epidemiol. 137: 1302–1317.

3. McCullough, M. L., Robertson, A. S., Rodriguez, C., Jacobs, E. J., Chai, A., Jonas, C., Calle, E. E., Willett, W. C. & Thun, M. J. (2003) Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). Cancer Causes Control 14: 1–12.

4. Wu, K., Willett, W. C., Fuchs, C. S., Colditz, G. & Giovannucci, E. (2002) Calcium intake and risk of colon cancer in women and men. J. Natl. Cancer Inst. 94: 437–436.

5. Bergsma-Kadijk, J. A., van't Veer, P., Kampman, E. & Burema, J. (1996) Calcium does not protect against colorectal neoplasia. Epidemiology 7: 590–597.

6. Grant, W. B. & Garland, C. F. (2004) A critical review of studies on vitamin D in relation to colorectal cancer. Nutr. Cancer 48: 115–123.

7. Martinez, M. E. & Willett, W. C. (1998) Calcium, vitamin D and colorectal cancer: a review of the epidemiologic evidence. Cancer Epidemiol. Biomark. Prev. 7: 163–169.

8. Bonithon-Kopp, C., Kronborg, O., Giacosa, A., Rath, U. & Faivre, J. (2000) Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. Lancet 356: 1300–1306.

9. Baron, J. A., Beach, M., Mandel, J. S., van Stolk, R. U., Haile, R. W., Sandler, R. S., Rothstein, R., Summers, R. W., Snover, D. C., Beck, G. J., Bond, J. H. & Greenberg, E. R. (1999) Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N. Engl. J. Med. 340: 101–107.

10. Hill, M. J., Morson, B.C. & Bussey, H. J. (1978) Aetiology of adenoma-carcinoma sequence in large bowel. Lancet 1: 245–247.

11. Sugarbaker, P. H., Gunderson, L. L. & Wittes, R. R. (1985) Colorectal cancer. In: Cancer: Principles and Practice of Oncology (DeVita, V. T., Hellman, S. & Roseeds, S. A., eds.), pp. 795–884. J. B. Lippincott, Philadelphia, PA.

12. Grau, M. V., Baron, J. A., Sandler, R. S., Haile, R. W., Beach, M. L., Church, T. R. & Heber, D. (2003) Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J. Natl. Cancer Inst. 95: 1765–1771.

13. Lanza, E., Schatzkin, A., Daston, C., Corle, D., Freedman, L., Ballard-Barbash, R., Caan, B., Lance, P., Marshall, J., Iber, F., Shike, M., Weissfeld, J., Slattery, M., Paskett, E., Mateski, D. & Albert, P. (2001) Implementation of a 4-y, high-fiber, high-fruit-and-vegetable, low-fat dietary intervention: results of dietary changes in the Polyp Prevention Trial. Am. J. Clin. Nutr. 74: 387–401.

14. Schatzkin, A., Lanza, E., Freedman, L. S., Tangrea, J., Cooper, M. R., Marshall, J. R., Murphy, P. A., Selby, J. V., Shike, M., Schade, R. R., Burt, R. W., Kikendall, J. W. & Cahill, J. (1996) The polyp prevention trial I: rationale, design, recruitment, and baseline participant characteristics. Cancer Epidemiol. Biomark. Prev. 5: 375–383.

15. Lanza, E., Schatzkin, A., Ballard-Barbash, R., Corle, D., Clifford, C., Paskett, E., Hayes, D., Bote, E., Caan, B., Shike, M., Weissfeld, J., Slattery, M., Mateski, D., Daston, C. & Clifford, D. C. (1996) The polyp prevention trial II: dietary intervention program and participant baseline dietary characteristics. Cancer Epidemiol. Biomark. Prev. 5: 385–392.

16. Schatzkin, A., Lanza, E., Corle, D., et al. (2000) Lack of effect of a low-fat high-fiber, fruit- and vegetable-enriched diet on the recurrence of colorectal adenomas. N. Engl. J. Med. 342: 1149–1155.

17. Block, G., Woods, M., Potosky, A. & Clifford, C. (1990) Validation of a self-administered diet history questionnaire using multiple diet records. J. Clin. Epidemiol. 43: 1327–1335.

18. SAS Institute Inc. (1996) SAS/STAT Software Changes and Enhancements through Release 6.11, pp. 807–884. SAS Institute, Cary, NC.

19. SAS Institute Inc. (1996) SAS/STAT User's Guide, Version 6. SAS Institute, Cary, NC.

20. Willett, W. & Stampfer, M. J. (1986) Total energy intake: implications for epidemiologic analyses. Am. J. Epidemiol. 124: 17–27.

21. Tangrea, J. A., Albert, P. S., Lanza, E., Woodson, K., Corle, D., Hasson, M., Burt, R., Caan, B., Paskett, E., Iber, F., Kirkendall, J. W., Shike, M., Weissfield, J. & Schatzkin, A. (2003) Non-steroidal anti-inflammatory drug use is associated with reduction in recurrence of advanced and non-advanced colorectal adenomas (United States). Cancer Causes Control 14: 403–411.

22. Panel on Calcium and Related Nutrients (1997) Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board Institute of Medicine. National Academy Press, Washington, DC.

23. Kampman, E., Slattery, M. L., Caan, B., & Potter, J. D. (2000) Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). Cancer Causes Control 11: 459–466.

24. White, E., Shannon, J. S. & Patterson, R. E. (1997) Relationship between vitamin and calcium supplement use and colon cancer. Cancer Epidemiol. Biomark. Prev. 6: 769–774.

25. Marcus, P. M. & Newcomb, P. A. (1998) The association of calcium and vitamin D, and colon and rectal cancer in Wisconsin women. Int. J. Epidemiol. 27: 788–793.

26. Boutron, M. C., Faivre, J., Marteau, P., Couillault, C., Senesse, P. & Quipourt, V. (1996) Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. Br. J. Cancer 74: 145–151.

27. Sellers, T. A., Bazyk, A. E., Bostick, R. M., Kushi, L. H., Olson, J. E., Anderson, K. E., Lazovich, D. & Folsom, A. R. (1998) Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). Cancer Causes Control 9: 357–367.

28. Gaard, M., Tretli, S. & Loken, E. B. (1996) Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. Eur. J. Cancer Prev. 5: 445–454.

29. Flood, A., Peters, U., Chatterjee, N., Lacey, J. V., Schairer, C. & Schatzkin, A. Calcium from diet and supplements is associated with reduced risk of colorectal cancer in a prospective cohort of women. Cancer Epidemiol. Biomark. Prev. (in press).

30. Cho, E., Smith-Warner, S. A., Spiegelman, D., Beeson, W. L., van den Brandt, P. A., Colditz, G. A., Folsom, A. R., Fraser, G. E., Freudenheim, J. L., Giovannucci, E., Goldbohm, R. A., Graham, S., Miller, A. B., Pietinen, P., Potter, J. D., Rohan, T. E., Terry, P., Toniolo, P., Virtanen, M. J., Willett, W. C., Wolk, A.,

Wu, K., Yaun, S.-S., Zeleniuch-Jacquotte, A. & Hunter, D. J. (2004) Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J. Natl. Cancer Inst. 96: 1015–1022.

31. Morimoto, L. M., Newcomb, P. A., Ulrich, C. M., Bostick, R. M., Lais, C. J. & Potter, J. D. (2002) Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential. Cancer Epidemiol. Biomark. Prev. 11: 1012–1018.

32. Nagata, C., Shimmizu, H., Kametani, M., Takeyama, N., Ohnuma, T. & Matsushita, S. (2001) Diet and colorectal adenoma in Japanese males and females. Dis. Colon Rectum 44: 105–111.

33. Benito, E., Cabeza, E., Moreno, V., Obrador, A. & Bosch, F. X. (1993) Diet and colorectal adenomas: a case-control study in Majorca. Int. J. Cancer 55: 213–219.

34. Breuer-Katschinski, B., Nemes, K., Marr, A., Rump, B., Leiendecker, B., Breuer, N., Goebell, H. & Colorectal Adenoma Study Group (2001) Colorectal adenomas and diet: a case-control study. Dig. Dis. Sci. 46: 86–95.

35. Lieberman, D. A., Prindiville, S., Weiss, D. G. & Willett, W. (2003) Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. J. Am. Med. Assoc. 290: 2959–2967.

36. Martinez, M. E., McPherson, R. S., Levin, B. & Glober, G. A. (1997) A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. Gastroenterology 113: 423–429.

37. Whelan, R. L., Horvath, K. D., Gleason, N. R., Forde, K. A., Treat, M. D., Teitelbaum, S. L., Bertram, A. & Neugut, A. I. (1999) Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. Dis. Colon Rectum 42: 212–217.

38. Peters, U., McGlynn, K. A., Chatterjee, N., Gunter, E., Garcia-Closas, M., Rothman, N. & Sinha, R. (2001) Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiol. Biomark. Prev. 10: 1267–1274.

39. Martinez, M. E., McPherson, R. S., Annegers, J. F. & Levin, B. (1996) Association of diet and colorectal adenomatous polyps: dietary fiber, calcium, and total fat. Epidemiology 7: 264–268.

40. Tseng, M., Murray, S. C., Kupper, L. L. & Sandler, R. S. (1996) Micronutrients and the risk of colorectal adenomas. Am. J. Epidemiol. 144: 1005–1014.

41. Martinez, M. E., Marshall, J. R., Sampliner, R., Wilkinson, J. & Alberts, D. S. (2002) Calcium, vitamin D, and risk of adenoma recurrence (United States). Cancer Causes Control 13: 213–220.

42. Hyman, J., Baron, J. A., Dain, B. J., Sandler, R. S., Haile, R. W., Mandel, J. S., Mott, L. A. & Greenberg, E. R. (1998) Dietary and supplemental calcium and the recurrence of colorectal adenomas. Cancer Epidemiol. Biomark. Prev. 7: 291–295.

43. Rozen, P., Lubin, F., Papo, N., Knaani, J., Farbstein, H., Farbstein, M. & Zajicek, G. (2001) Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. Cancer 91: 833–840.

44. Cats, A., Kleibeuker, J. H., van der Meer, R., Kuipers, F., Sluiter, W. J., Hardonk, M. J., Oremus, E. T., Mulder, N. H. & de Vries, E. G. (1995) Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. J. Natl. Cancer Inst. 87: 598–603.

45. Holt, P. R., Atillasoy, E. O., Gilman, J., Guss, J., Moss, S. F., Newmark, H., Fan, K., Yang, K. & Lipkin, M. (1998) Modulation of abnormal colonic epithelial cell proliferation and differentiation by low-fat dairy foods: a randomized controlled trial. J. Am. Med. Assoc. 280: 1074–1079.

46. Neugut, A. I., Horvath, K., Whelan, R. L., Terry, M. B., Garbowski, G. C., Bertram, A., Forde, K. A., Treat, M. R. & Waye, J. (1996) The effect of calcium and vitamin supplements on the incidence and recurrence of colorectal adenomatous polyps. Cancer 78: 723–728.

47. Wallace, K., Baron, J. A., Cole, B. F., Sandler, R. S., Karagas, M. R., Beach, M. A., Haile, R. W., Burke, C. A., Pearson, L. H., Mandel, J. S., Rothstein, R. & Snover, D. S. (2004) Effect of calcium supplementation on the risk of large bowel polyps. J. Natl. Cancer Inst. 96: 921–925.

48. Peters, U., Chatterjee, N., Yeager, M., Chanock, S., Schoen, R. E., McGlynn, K. A., Church, T. R., Weisfelt, J., Schatzkin, A. & Hayes, R. B. (2004) Association of genetic variants in the calcium-sensing receptor with risk of colorectal adenoma. Cancer Epidemiol. Biomark. Prev. 13: 546–552.

49. McCarty, M. F. (2003) A moderately low phosphate intake may provide health benefits analogous to those conferred by UV light—a further advantage of vegan diets. Med. Hypoth. 61: 543–560.

APPENDIX

The members of the Polyp Prevention Study Group participated in the conduct of the Polyp Prevention Trial. However, the data presented in this manuscript and the conclusions drawn from them are solely the responsibility of the coauthors listed for the paper.

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